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(54) Title: (HETERO)ARYL-SULPONAMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS FACTOR XA INHIBITORS			
$\begin{array}{c} \text{NR}_2\text{R}_3 \\ \\ \text{A}-\text{S}-\text{C}-\text{NR}-\text{C}(=\text{O})-\text{CH}_2-\text{NR}-\text{SO}_2\text{Q} \\ \\ \text{H} \end{array} \quad (1)$			
(57) Abstract			
<p>A compound of formula (1), or a pharmaceutically-acceptable salt thereof, wherein A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur; B is optionally substituted phenylene or a 6-membered heterocyclic ring containing 1, 2 or 3 nitrogen heteroatoms; R and R₁ are independently selected from hydrogen and (1-4C)alkyl; n is 1 or 2; R₂ and R₃ are independently selected from hydrogen, (1-6C)alkyl, (4-7C)cycloalkyl, (2-6C)alkenyl or R₂ and R₃ may form along with the nitrogen to which they are attached a 5-, 6- or 7-membered heterocyclic ring which may contain in addition to the nitrogen atom present 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur, wherein each R₂ or R₃ group or any heterocyclic ring formed from R₂ and R₃ may be optionally substituted by hydroxy, amino, carboxy, (1-4C)alkoxycarbonyl, oxo, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, or carbamoyl-(1-4C)alkyl; Q is selected from phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl and a 5-, 6- or 7-membered heterocyclic ring containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur wherein Q may be optionally substituted by halo, halo(1-4C)alkyl, cyano, amino, hydroxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (2-4C)alkoxyl, (2-4C)alkoxyl, (1-4C)alkylthio, (1-4C)alkylsulphimyl, (1-4C)alkylsulphonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, (2-6C)alkanoyl, (2-4C)alkanoylarnino, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carbony-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, phenoxy, phenylthio, phenylsulphimyl, phenylsulphonyl, benzyl or benzoyl substituent bears 1, 2 or 3 substituents selected from halo, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-(1-4C)alkylcarbamoyl and (2-4C)alkenylamino, which possesses antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention relates to processes for the preparation of the heterocyclic derivative, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.</p>			

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(HETERO)ARYL-SULFONAMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS FACTOR XA INHIBITORS

The invention relates to heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.

The antithrombotic and anticoagulant effect produced by the compounds of the invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

15 Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by R.B. Wallis, Current Opinion in Therapeutic Patents, 1993, 1173-1179. Thus it is known that two proteins, one known as antistatin and the other known as tick anticoagulant protein (TAP), are specific Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

20 It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by R.B. Wallis, all possessed a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that certain heterocyclic derivatives possess Factor Xa inhibitory activity. Many of the compounds of the present invention also possess the advantage of being selective Factor Xa inhibitors, that is the enzyme Factor Xa is inhibited strongly at concentrations of test compound which do not inhibit or which inhibit to a lesser extent the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

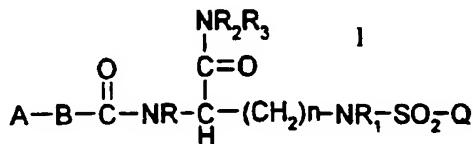
30 The compounds of the present invention possess activity in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated, for

example in the treatment or prevention of thrombotic conditions such as coronary artery and cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular 5 injury including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischaemia and angina 10 (including unstable angina).

The compounds of the invention are also useful as inhibitors of blood coagulation in an ex-vivo situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

Accordingly in one aspect the present invention provides compounds of formula I

15



wherein:

20 A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur;

B is optionally substituted phenylene or a 6-membered heterocyclic ring containing 1, 2 or 3 nitrogen heteroatoms;

R and R₁ are independently selected from hydrogen and (1-4C)alkyl;

25 n is 1 or 2;

R₂ and R₃ are independently selected from hydrogen, (1-6C)alkyl,

(4-7C)cycloalkyl, (2-6C)alkenyl on R₂ and R₃ may form along with the nitrogen to which they are attached a 5-, 6- or 7- membered heterocyclic ring which may contain in addition to the nitrogen atom present 1 or 2 additional heteroatoms selected from nitrogen, oxygen

and sulphur, wherein each R₂ or R₃ group or any heterocyclic ring formed from R₂ and R₃ may be optionally substituted by hydroxy, amino, carboxy, (1-4C)alkoxycarbonyl, o xo, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, or carbamoyl-(1-4C)alkyl;

5 Q is selected from phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl and a 5-, 6- or 7- membered heterocyclic ring containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur wherein Q may be optionally substituted by halo, halo(1-4C)alkyl, cyano, amino, hydroxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyoxy, (1-4C)alkylthio, 10 (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbonoyl, (2-6C)alkanoyl, (2-4C)alkanoylamino, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, phenoxy, phenylthio, 15 phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl wherein said phenyl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl or benzoyl substituent bears 1, 2 or 3 substituents selected from halo, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-(1-4C)alkylcarbamoyl and 20 (2-4C)alkenoylamino, or a pharmaceutically acceptable salt thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

It is to be understood that certain heterocyclic derivatives of the present invention 25 can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Factor Xa inhibitory activity.

It is further to be understood that, insofar as certain of the compounds of the formula defined above may exist in optically active or racemic forms by virtue of one or 30 more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which possesses Factor Xa inhibitory activity. The synthesis of optically

active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Preferably A is a pyridyl, pyrimidinyl or pyridazinyl ring for example 4-pyridyl.

5 2-pyridyl, 4-pyridazinyl, 3-pyrimidinyl, 4-pyrimidinyl or 3-pyridyl. Of these 4-pyrimidinyl and 4-pyridyl are most preferred.

In one aspect A is unsubstituted. In another aspect A is substituted by one, two or three atoms or groups selected from halo (for example fluoro, chloro or bromo), oxo, carboxy, trifluoromethyl, cyano, amino, hydroxy, nitro, (1-4C)alkyl (for example methyl or 10 ethyl), (1-4C)alkoxy (for example methoxy or ethoxy), (1-4C)alkoxycarbonyl (1-4C)alkylamino (for example methylamino or ethylamino) or di-(1-4C)alkylamino (for example dimethylamino or diethylamino). For the avoidance of doubt substituents on A may also be present, where possible, on the heteroatom of the ring. Preferred substituents of A are halo, (1-4C)alkyl, amino and (1-4C)alkylamino.

15 There are three preferred aspects of ring B:

1. In one aspect B is an optionally substituted 1,4-phenylene ring
2. In one aspect B is an optionally substituted 1,4-piperidinediyl ring, wherein A or the carbonyl group (-CO-) on either side of B is attached to the nitrogen atom of the ring or B is an optionally substituted 1,4-piperazinediyl ring, wherein both 20 A and the carbonyl group (-CO-) on either side of B are attached to the nitrogen atoms atoms of the ring.
3. In one aspect B is a heterocyclic ring in which neither A nor the carbonyl group (-CO-) on either side of B are not attached to nitrogen atom(s) of B.

25 In a preferred aspect heterocyclic rings formed from R₂ and R₃ include

1-piperidino, 1-piperazinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolidinyl and 1-pyrrrolidinyl; preferred substitutions include oxo, hydroxy, amino and carboxy and include substitutions on any of the additional heteroatoms, for example 1-oxo-4-thiomorpholino and 1,1-dioxo-4-thiomorpholino.

30 In a preferred aspect R and R₁ are both hydrogen.

A suitable value for Q when it is naphthyl is, for example, 1-naphthyl or

2-naphthyl; when it is phenyl-(1-4C)alkyl is, for example, benzyl, phenylethyl and 3-phenylpropyl, when it is phenyl-(2-4C)alkenyl is, for example, styryl, cinnamyl or 3-phenylprop-2-enyl; and when it is phenyl-(2-4C)alkynyl is, for example, 2-phenylethynyl, 3-phenylprop-2-ynyl and 3-phenylprop-1-ynyl.

5 A suitable value for Q when it is a heterocyclic moiety containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur is, for example, a 5- or 6-membered heterocyclic moiety which is a single ring or is fused to one or two benzene rings such as furyl, benzofuranyl, tetrahydrofuryl, chromanyl, thienyl, benzothienyl, pyridyl, piperidinyl, quinolyl, 1,2,3,4-tetrahydroquinolanyl, isoquinolyl, 1,2,3,4-tetrahydroisoquinolanyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pyrrolyl, pyrrolidinyl, indolyl, indolinyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, morpholinol, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl, thiadiazolyl, tetrazolyl, 15 dibenzofuranyl and dibenzothienyl, which may be attached through any available position including, for an appropriate X₂ group such as, for example, SO₂, C(R³)₂ or CO, through any available nitrogen atom and which may bear up to three substituents including a substituent on any available nitrogen atom.

A suitable value for the heteroaryl substituent on Q or the heteroaryl group in a 20 heteroaryl-containing substituent on Q which comprises a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur is, for example, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl and thiadiazolyl which may be attached through any 25 available position including through any available nitrogen atom.

Particularly preferred substituents of Q are selected from halo (ideally chloro or bromo) and C₁₋₄alkyl (ideally methyl).

Suitable values for optional substituents for B, Q and for R₁ and R₃ are:

for (1-4C)alkyl: methyl, ethyl and propyl;

30 for (1-4C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl,

propoxycarbonyl and tert-butoxycarbonyl;

	for hydroxy-(1-4C)alkyl:	hydroxymethyl, 1-hydroxyethyl,
		2-hydroxyethyl and 3-hydroxypropyl;
	for (1-4C)alkoxy-(1-4C)alkyl:	methoxymethyl, ethoxymethyl,
5		1-methoxymethyl, 2-methoxyethyl,
	for carboxy-(1-4C)alkyl:	2-ethoxyethyl and 3-methoxypropyl;
		carboxymethyl, 1-carboxyethyl,
	for (1-4C)alkoxycarbonyl-(1-4C)alkyl:	2-carboxyethyl and 3-carboxypropyl;
		methoxycarbonylmethyl,
10		ethoxycarbonylmethyl, <u>tert</u> -butoxy-
		carbonylmethyl, 1-methoxycarbonylethyl,
		1-ethoxycarbonylethyl,
		2-methoxycarbonylethyl,
		2-ethoxycarbonylethyl,
		3-methoxycarbonylpropyl and
15		3-ethoxycarbonylpropyl;
	for carbamoyl-(1-4C)alkyl:	carbamoylmethyl, 1-carbamoylethyl,
		2-carbamoylethyl and
		3-carbamoylpropyl;

20 Suitable values for substituents (where applicable) which may be present on B, on a heterocyclic or phenyl group within a substituent on Ar, on Q or on a phenyl- or heteroaryl-containing substituent on Q include, for example:-

	for halo:	fluoro, chloro, bromo;
25	for (1-4C)alkyl:	methyl, ethyl, propyl, butyl;
	for (1-4C)alkoxy:	methoxy, ethoxy;
	for (1-4C)alkylamino:	methylamino, ethylamino;
	for di-(1-4C)alkylamino:	dimethylamino, diethylamino;
	for (2-4C)alkenyl:	vinyl and allyl;
30	for (2-4C)alkynyl:	ethynyl and prop-2-ynyl;
	for (2-4C)alkenyloxy:	vinyloxy and allyloxy;

for (2-4C)alkynyloxy:
for 4-(1-4C)alkylpiperazin-1-yl:

for (1-4C)alkylthio:
5 for (1-4C)alkylsulphinyl:

for (1-4C)alkylsulphonyl:

for (2-4C)alkanoylamino:
10 for (1-4C)alkanesulphonamido:

for (1-4C)alkoxycarbonyl:

for N-(1-4C)alkylcarbamoyl:
15 for N,N-di-[(1-4C)alkyl]carbamoyl:

for 4-(1-4C)alkylpiperazin-1-ylcarbonyl:
20 for (1-4C)alkanesulphonamidocarbonyl:

for (2-4C)alkanoyl:
for hydroxy-(1-4C)alkyl:
25 for (1-4C)alkoxy-(1-4C)alkyl:

for carboxy-(1-4C)alkyl:
30

ethynyloxy and prop-2-nyloxy;
4-methylpiperazin-1-yl and
4-ethylpiperazin-1-yl;
methylthio, ethylthio and propylthio;
methylsulphinyl, ethylsulphinyl and
propylsulphinyl;
methylsulphonyl, ethylsulphonyl and
propylsulphonyl;
acetamido, propionamido and butyramido;
methanesulphonamido and
ethanesulphonamido:
methoxycarbonyl, ethoxycarbonyl,
propoxycarbonyl and tert-butoxycarbonyl;
N-methylcarbamoyl, N-ethylcarbamoyl and
N-propylcarbamoyl;
N,N-dimethylcarbamoyl,
N-ethyl-N-methylcarbamoyl and
N,N-diethylcarbamoyl;
4-methylpiperazin-1-ylcarbonyl and
4-ethylpiperazin-1-ylcarbonyl;
methanesulphonamidocarbonyl and
ethanesulphonamidocarbonyl;
acetyl, propionyl and butyryl;
hydroxymethyl, 1-hydroxyethyl,
2-hydroxyethyl and 3-hydroxypropyl;
methoxymethyl, ethoxymethyl,
1-methoxymethyl, 2-methoxyethyl,
2-ethoxyethyl and 3-methoxypropyl;
carboxymethyl, 1-carboxyethyl,
2-carboxyethyl and 3-carboxypropyl;

for (1-4C)alkoxycarbonyl-

(1-4C)alkyl:

methoxycarbonylmethyl,
ethoxycarbonylmethyl, tert-butoxy-
carbonylmethyl, 1-methoxycarbonylethyl,

5

1-ethoxycarbonylethyl,

2-methoxycarbonylethyl,

2-ethoxycarbonylethyl,

3-methoxycarbonylpropyl and

3-ethoxycarbonylpropyl;

10 for carbamoyl-(1-4C)alkyl:

carbamoylmethyl, 1-carbamoylethyl,

2-carbamoylethyl and 3-carbamoylpropyl;

for N-(1-4C)alkylcarbamoyl-(1-4C)alkyl:

N-methylcarbamoylmethyl,

N-ethylcarbamoylmethyl,

N-propylcarbamoylmethyl,

15

1-(N-methylcarbamoyl)ethyl,

1-(N-ethylcarbamoyl)ethyl,

2-(N-methylcarbamoyl)ethyl,

2-(N-ethylcarbamoyl)ethyl and

3-(N-methylcarbamoyl)propyl;

20 for N,N-di-[(1-4C)alkyl]carbamoyl-

(1-4C)alkyl:

N,N-dimethylcarbamoylmethyl,

N-ethyl-N-methylcarbamoylmethyl,

N,N-diethylcarbamoylmethyl,

1-(N,N-dimethylcarbamoyl)ethyl,

1-(N,N-diethylcarbamoyl)ethyl,

2-(N,N-dimethylcarbamoyl)ethyl,

2-(N,N-diethylcarbamoyl)ethyl and

3-(N,N-dimethylcarbamoyl)propyl;

25

A preferred class of compounds of the present invention is that wherein:

30

A is pyridyl, pyrimidinyl or pyridazinyl;

B is 1,4-piperidinediyl, 1,4-piperazinediyl or para-phenylene;

R₂ and R₃ are joined together to form a 6-membered heterocyclic ring, preferably substituted;

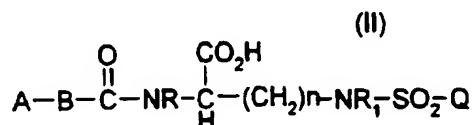
5 Q is styryl or naphthyl optionally substituted by fluoro, chloro or bromo or is phenyl optionally substituted by fluoro, chloro or bromo; and pharmaceutically-acceptable salts thereof.

Particular compounds of the invention are those listed as Examples below.

10 A heterocyclic derivative of formula I, or pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of related compounds. Such procedures are provided as a further feature of the invention and are illustrated by the following representative processes in which, unless otherwise stated A, B, X₁, R, R₁, R₂, R₃ and Q have any of the meanings defined hereinbefore wherein any 15 functional group, for example amino, alkylamino, carboxy or hydroxy, is optionally protected by a protecting group which may be removed when necessary.

Compounds of formula I may be prepared by:

20 (a) Reacting an acid of formula (II), or a reactive derivative thereof.



with an amine of formula (III) R₂R₃NH

25 A suitable reactive derivative of an acid of the formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated amide such as 1,1'-carbonyldiimidazole; an active

ester, for example an ester formed by the reaction of the acid and a ph nol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole or N-hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl 5 cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide.

The reaction is conveniently carried out in the presence of a suitable base such

10 as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic 15 amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene.

The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide.

20 N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an 25 arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for 30 example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid

such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative 5 protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an 10 arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a 15 benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

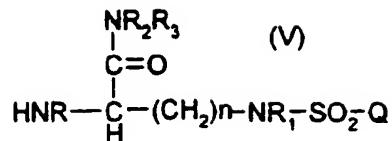
A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which 20 may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

(b) Reacting an acid of formula (IV), or a reactive derivative thereof,

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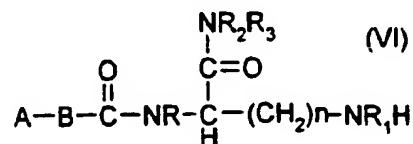
with an amine of formula (V)



Suitable reactive derivatives of an acid of the formula (IV) and conditions are described in process method (a) above.

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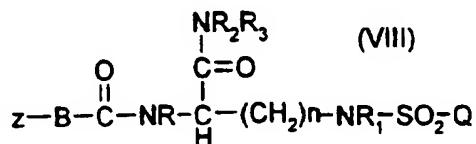
(c) Coupling a compound of formula (VI)



10 with a compound of formula (VII) $\text{Z}-\text{SO}_2\text{Q}$

wherein Z is a displaceable group such as halo, in conditions similar to those described in process method (a) above.

(d) For compounds of formula I, wherein A is attached to B by an alkyl bond, by coupling 15 a compound of formula (VIII)



wherein Z is a displaceable group such as halo, with an activated derivative of heterocyclic ring A. Suitable activated derivatives include metalised derivatives such as with zinc or tin and borane derivatives. The activated derivative of heterocyclic ring A is reacted with a 20 compound of formula (VII) to effect cross coupling where Z is a halo group, such as iodo, bromo or chloro, or triflate. Suitably the reaction is catalysed by use of a transition state metal catalyst, such as palladium, e.g. tetrakis (triphenylphosphine) palladium (0).

Alternatively it is possible that ring A contains the displaceable group Z and ring B is activated and the reaction performed as described above.

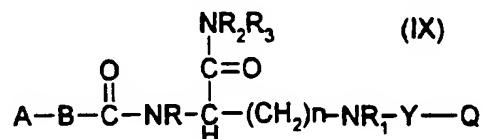
(e) For compounds of formula I, wherein A is attached to B by an alkyl bond, by forming A ring on compounds of formula (VIII), wherein Z is a functional group capable of cyclisation. Suitable reagents and conditions are described below in the preparation of compounds of formula (IV) by cyclisation.

5

(f) For compounds of formula I, wherein A is attached to B by an amide bond, by reacting an amine of formula (VIII), wherein Z is hydrogen, with a derivative of heterocyclic ring A containing a suitable displaceable group, such as halo, in the presence of a base in conditions similar to those described in process method (a) above.

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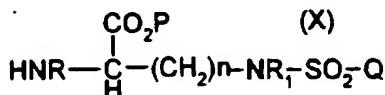
(g) Oxidation of a compound of formula (IX)



15 wherein Y is S or SO.

A suitable oxidising agent is, for example, any agent known in the art for the oxidation of thio to sulphanyl and/or sulphonyl, for example, hydrogen peroxide, a peracid (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxy sulphate (such as potassium peroxy monosulphate), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidising agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a suitable solvent or diluent such as methylene chloride, chloroform, acetone, tetrahydrofuran or *tert*-butyl methyl ether and at a temperature, for example, at or near ambient temperature, that is in the range 15 to 35°C. Those compounds of formula (IX) which contain oxygen labile groups (such as A ring is pyridyl) are probably not suitable intermediates for this process step, unless oxidation of such groups is desired.

Compounds of formula (II) may be prepared by reacting an acid of formula (IV), as defined above, with an amine of formula (X)



5

wherein P, including the carboxy group to which it is attached, is a suitable protecting group such as an alkoxy ester, for example ethoxycarbonyl; in an analogous method as described in process method (b) above, and subsequently conversion to the acid compound of formula (II) by deesterification.

10 Compounds of formula (IV) may be prepared by coupling of the B ring to the A ring as described in alternative process steps (d) and (f). For a coupling of A to B, via an alkyl bond, one ring is activated and the other contains a suitable displaceable group. Ideally the reaction is catalysed, such as with a palladium catalyst. Suitable reagents and conditions are described in a review article Harvey R.G. *Organic Preparations and*
 15 *Procedures International*, Vol.29,(1997). 139.

Activated derivatives of heterocyclic ring A or B include metalised derivatives, such as with zinc or tin, borane derivatives and stannyli derivatives. Formation of the activated form desired is typically by substitution reactions. The activating group is added to the ring in place of a suitable leaving group or atom, such as halo or triflate. Suitable 20 reagents and conditions are described in Shikara M. et.al.; *Chem. Pharm. Bull.*; 33(11), 4755-4763 (1985); Sandosham J. et.al.: *Heterocycles*, Vol.37, No.1, p501, (1994); and Salamoto T. et.al.; *Tetrahedron*; Vol.49, No.43, 9713-9720, (1993).

Alternatively compounds of formula (IV) may be prepared as described in process variant (e) above by forming A rings on the B ring containing a suitable 25 functional group for cyclisation. Suitable reagents and conditions are described in Bredereck H. *Chem.Ber.*; 96, 1505, (1963); Fuchigami, T., *Bull. Chem. Soc. Jpn.* 49, p3607, (1976); Huffman, K.R., *J. Org. Chem.*, 28, p1812, (1963); Palusso, G., *Gazz. Chim. Ital.*, 90, p1290, (1960) and Ainsworth C.J., *Heterocycl. Chem.*, 3, p470, (1966). Processes suitable for synthesis of starting materials in such cyclisation reactions are

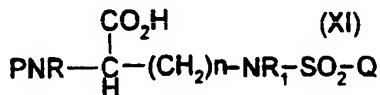
- 15 -

described in Zhang M.Q. et.al; J.Heterocyclic. Chem.; 28, 673, (1991) and Kosugi. M. et al., Bull. Chem. Soc. Jpn., 60, 767-768 (1987).

Compounds of formula (XII) may be prepared via ring formation, such as described in Church R. et.al.; J.Org.Chem., 60, 3750-3758, (1995) and Falck-Penderson 5 M.L. et.al.; Acta Chem. Scand., 47, 63-67, (1993). Compounds formed by such reactions are also suitable starting materials for preparation of activated derivatives of the heterocyclic ring A by substitution reaction, as described above.

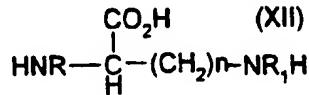
Compounds of formula (V) may be prepared by reacting an acid of formula (XI)

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wherein P is a protecting group, with an amine of formula (III), as defined above, in an analogous manner as described in method (a) above, and subsequently removing the 15 protecting group.

Compounds of formula (VI) may be prepared from the amino acid of formula (XII)



20 by performing both reactions (a) and (b) described above, in either order, with the use of suitable protecting groups as described above.

Compounds of formula (VII) may be prepared by conversion of the thio analogue of the compound of formula (XIII), wherein Z is a dispaceable group

25



to the sulphonic acid halide by reactions as described in Kharasch N. Et.al.; J.Am.Chem.Soc., 73, p3240, 1951. Suitable reactions for the preparation of the thio

analogues of compounds of formula (VII) are described in Newman M.S. et.al.; *Organic Synthesis*. Vol. 51, p139.

Compounds of formula (VIII) may be prepared from compounds of formula (XII), as defined above, by performing reaction (a) described above and reacting the 5 product with an acid of formula (XIV) Z-B-COOH in conditions similar to those described for reaction (b) above.

Compounds of formula (IX) may be prepared by an analogous reaction for the preparation of compounds of formula I using method (c) above, reacting a compound of formula (VI), as defined above, with a compound of formula (XIII), as defined above.

10 When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure.

15 When an optically active form of a compound of the formula I is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure.

As stated previously, the compounds of the formula I are inhibitors of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or more of the standard procedures set out hereinafter:-

20

a) Measurement of Factor Xa Inhibition

An in vitro assay system is carried out based on the method of Kettner et al., *J. Biol. Chem.* 1990, 265, 18289-18297, whereby various concentrations of a test compound are dissolved in a pH7.5 buffer containing 0.5% of a polyethylene glycol (PEG 6000) and 25 incubated at 37°C with human Factor Xa (0.001 Units/ml, 0.3 ml) for 15 minutes. The chromogenic substrate S-2765 (KabiVitrum AB, 20 µM) is added and the mixture is incubated at 37°C for 20 minutes whilst the absorbance at 405 nm is measured. The maximum reaction velocity (V_{max}) is determined and compared with that of a control sample containing no test compound. Inhibitor potency is expressed as an IC₅₀ value.

30

b) Measurement of Thrombin Inhibition

The procedure of method a) is repeated except that human thrombin (0.005 Units/ml) and the chromogenic substrate S-2238 (KabiVitrum AB, 7 μ M) are employed.

c) Measurement of Anticoagulant Activity

5 An in vitro assay whereby human, rat or rabbit venous blood is collected and added directly to a sodium citrate solution (3.2 g/100 ml, 9 parts blood to 1 part citrate solution). Blood plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at 2-4°C. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to 10 double the clotting time, hereinafter referred to as CT2, is determined. In the PT test, the test compound and blood plasma are incubated at 37°C for 10 minutes. Tissue thromboplastin with calcium (Sigma Limited, Poole, England) is added and fibrin formation and the time required for a clot to form are determined.

(d) Rat Disseminated Intravascular Coagulation *in vivo* activity test

15 Fasted male Alderley Park rats (300-450 g) are pre-dosed by oral gavage (5 mls/kg) with compound or vehicle (5% DMSO/PEG200) at various times before being anaesthetised with Intraval® (120 mg/kg i.p.). The left jugular vein and the right carotid artery are exposed and cannulated. A 1 mL blood sample is taken from the carotid canular into 3.2% 20 trisodium citrate. 0.5 mL of the whole blood is then treated with EDTA and used for platelet count determination whilst the remainder is centrifuged (5 mins, 20000g) and the resultant plasma frozen for subsequent drug level, fibrinogen or thrombin antithrombin (TAT) complex determinations. Recombinant human tissue factor (Dade Innovin Cat.B4212-50), reconstituted to the manufacturers specification, is infused (2 mL/kg/hr) 25 into the venous canular for 60 minutes. Immediately after the infusion is stopped a 2 mL blood sample is taken and platelet count, drug level, plasma fibrinogen concentration and TAT complex are determined as before. Platelet counting is performed using a Coulter TS40 blood analyser. Plasma fibrinogen and TAT levels are determined using a clotting assay (Sigma Cat.880-B) and TAT ELISA (Behring) respectively. The plasma 30 concentration of the compound is bioassayed using human Factor Xa and a chromogenic substrate S2765 (Kabi), extrapolated from a standard curve (Fragmin) and expressed in Anti-Factor Xa units. The data is analysed as follows: tissue factor-induced reductions in

platelet count are normalised with respect to pre-dose platelet count and drug activity expressed as a percent inhibition of tissue factor-induced thrombocytopenia when compared to vehicle treated animals. Compounds are active if there is statistically significant ($p < 0.05$) inhibition of TF-induced thrombocytopenia.

5 c) An ex vivo Assay of Anticoagulant Activity

The test compound is administered intravenously or orally to a group of Alderley Park Wistar rats. At various times thereafter animals are anaesthetised, blood is collected and PT coagulation assays analogous to those described hereinbefore are conducted.

10 According to a further feature of the invention there is provided a pharmaceutical composition which comprises a heterocyclic derivative of the formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, 15 capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for 20 example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a heterocyclic derivative of the formula 25 I, or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients 30 which may vary from about 5 to about 98 percent by weight of the total composition.

Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided a heterocyclic derivative of formula I, or a pharmaceutically acceptable salt thereof, for use in medical 5 therapy.

According to a further feature of the invention there is provided a heterocyclic derivative of formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes the use of such an active ingredient in the 10 production of a medicament for use in:-

- (i) producing a Factor Xa inhibitory effect;
- (ii) producing an anticoagulant effect;
- (iii) producing an antithrombotic effect;
- (iv) treating a Factor Xa mediated disease or medical condition;
- 15 (v) treating a thrombosis mediated disease or medical condition;
- (vi) treating coagulation disorders; and/or
- (vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined 20 hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of an active ingredient as defined hereinbefore.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the medical 25 condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the formula I are useful in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated. In using a compound of the formula I for such a purpose, it will generally be administered so that a daily dose in the 30 range, for example, 0.5 to 500 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed.

for example a dose for intravenous administration in the range, for example, 0.5 to 50 mg/kg body weight will generally be used. For preferred and especially preferred compounds of the invention, in general, lower doses will be employed, for example a daily dose in the range, for example, 0.5 to 10 mg/kg body weight.

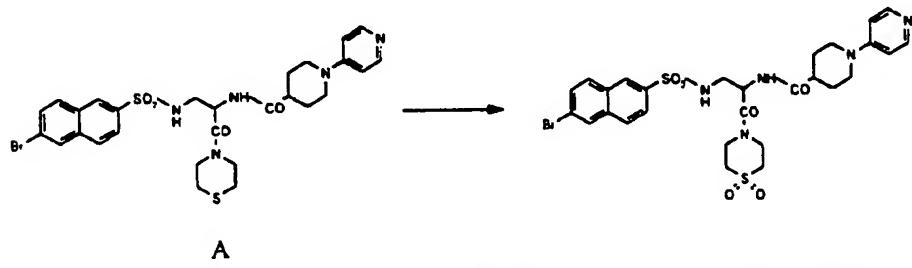
5 Although the compounds of the formula I are primarily of value as therapeutic or prophylactic agents for use in warm-blooded animals including man, they are also useful whenever it is required to produce an anticoagulant effect, for example during the ex-vivo storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

10 The compounds of the invention may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane 15 antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

Example 1

1-(1,1-Dioxothiomorpholino-4-carbonyl)-1-[1-(4-pyridyl)piperazin-4-
ylcarbamoyl]-2-(bromonaphth-2-ylsulphonamido)ethane

Method I



25 To a stirred suspension of A, prepared as in Example 2, (1.00g, 1.548mmole) in chloroform (50ml) at room temperature was added metachloroperbenzoic acid (1.597g, 4.644mmole, 3 equivalents). A yellow gum formed. This gum was washed with dichloromethane (150 ml) and then with water (100ml). The resulting yellow solid was

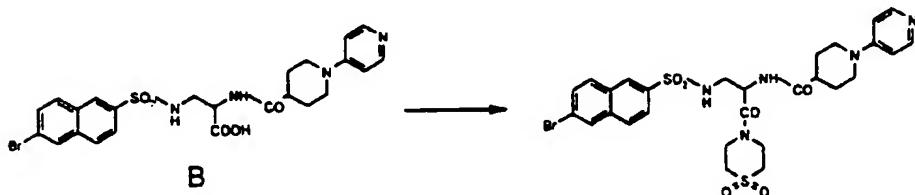
triturated with ether and was dried in vacuo to give a pale yellow solid. This material was chromatographed on an alumina bond elute column, eluting with dichloromethane with increasing concentrations of methanol from 0% to 5%. The required product was eluted with 2% to 3% methanol in dichloromethane. Evaporation of these fractions yielded the 5 product as a colourless solid (0.30g, 28%).

NMR (300MHz,DMSO) 1.4-1.6(m,2H); 1.6-1.7(m,2H); 2.3-2.4(m,1H); 2.7-2.8(m,2H); 2.9-3.3(m,5H); 3.7-4.0(m,6H); 4.7-4.9(m,1H); 6.7-6.8(m,2H); 7.7-7.9(m,3H); 8.0-8.2(m,5H); 8.3(s,1H); 8.5(s,1H)

MS ES⁺ (mH)⁺ 678

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Method 2



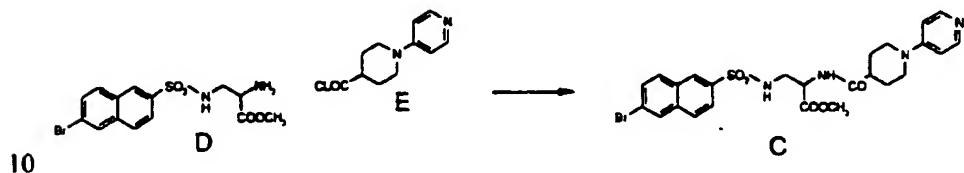
EDAC (10.283g, 53.6mmole) was added to a solution of B (35g, 44.7mmole), 15 thiomorpholine sulphone trifluoroacetate (13.36g, 53.6mmole), n-hydroxybenztriazole (9.052g, 67mmole) and triethylamine(6.94ml) in DMF (500ml). Stirring was continued overnight. The mixture was poured into water (3.5litres) and basified to pH8 with aqueous sodium hydroxide (2M). A white solid precipitated which was filtered off. The solid was dissolved in a mixture of dichloromethane and methanol (1:1 by volume). The resulting 20 solution was boiled on the steam bath to reduce the volume until the solution became slightly cloudy. On cooling the required product separated as colourless crystals. The product was filtered off, washed with ether and dried.

The starting materials were prepared as follows;



Sodium hydroxide (1M, 38.7ml, 38.7mmole) was added to a stirred solution of C (7.42g, 12.9mmole) in methanol (77ml). After 1 hour the resulting solution was warmed 5 and boiled under reflux for 0.75 hour, and then was allowed to cool to room temperature and stirred for a further 1 hour. The solution was acidified with 2M hydrochloric acid, and was evaporated in vacuo to yield B as a colourless solid (8.83g, 82%).

MS ESP- (m-H)- 559



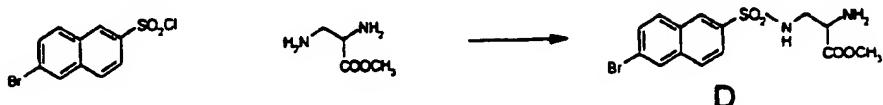
Thionyl chloride (10.54ml, 144.6mmole) was added to a stirred suspension of N-(4-pyridyl)piperidine-4-carboxylic acid (3.7245g, 18.08mmole) in dichloromethane (50ml). Stirring was continued for 2 hours. The solvent was evaporated in vacuo and the residue 15 re-evaporated from dichloromethane (3X50ml) to leave the product E. A solution of this acid chloride in dichloromethane (50ml) was added slowly to a stirred solution D chloride (7.0g, 18.08mmole) and triethylamine (7.546ml, 54.2mmole) in dichloromethane, and the resulting mixture was stirred overnight. The solution was poured into water (500ml) and the resulting mixture was extracted with dichloromethane (3X100ml). The combined 20 extracts were dried over magnesium sulphate, and evaporated to leave a yellow oil. This was chromatographed on a column of deactivated alumina (100g), eluting with dichloromethane containing 1%, 2% and finally 3% methanol by volume. The fractions containing the required product C were evaporated in vacuo to afford a pale yellow foam (7.42g, 71%).

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NMR (300MHz, DMSO) 1.4-1.5(m,2H); 1.6-1.7(m,2H); 2.3-2.4(m,1H); 2.7-2.9(m,2H); 3.1-3.2(m,2H); 3.55(s,3H); 3.8-3.9(m,2H); 4.3-4.4(m,1H); 6.75(d,2H); 7.75-7.85(m,2H); 7.9-8.0(m,1H); 8.1-8.2(m,5H); 8.35(s,1H); 8.45(s,1H)

MS ESP+ (mH)+ 575

5



A solution of 6-bromonaphthalene-2-sulphonyl chloride (19.17g, 71mmole) in dichloromethane (150ml) was added over 0.5 hour to a stirred mixture of methyl 2,3-diaminopropionate dihydrochloride (13.561g, 71mmole) and triethylamine 29.63ml, 213mmole) in dichloromethane (400ml) at 0°C. The solid gradually dissolved. The mixture was stirred at 0°C for 1 hour and overnight at room temperature. The yellow solution was washed with water (2x350ml). The combined extracts were dried over magnesium sulphate, and the solvent evaporated in vacuo to leave a brown residue. This was dissolved in methanol (500ml) and hydrogen chloride in ether (100ml, 1M) was added. The solution was stirred for 1 hour, and was then evaporated in vacuo to leave a brown solid. Ethyl acetate (300ml) was added and the mixture warmed to reflux. The brown solid changed in appearance to a colourless solid. The suspension was cooled and stirred at 0°C for 10 minutes. The required product D was filtered off (16.26g, 54%).

NMR (300MHz, DMSO) 3.2-3.3(m,2H); 3.7(s,3H); 4.1(t,1H); 7.8(dd,1H); 7.9(dd,1H); 8.15(d,2H); 8.35(s,1H); 8.5(s,1H); 8.6-8.8(m,3H)

MS ESP+ (mH)+ 387



25

Thionyl chloride (22ml) was added over 10 minutes to methanol (360ml) at -5°C with stirring. After stirring for a further 5 minutes at -5°C, 2,3-diaminopropionic acid monohydrochloride (10g, 71mmole) was added. The mixture was stirred at -5°C for 3

hours, at which time all of the solid had dissolved. After stirring at room temperature for 2 hours, the solution was boiled under reflux for 1.5 hours, and was stood at room temperature overnight. Evaporation of the solvent in vacuo afforded the required product as colourless crystals (13.56g. 100%).

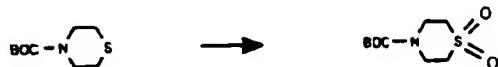
5 NMR (300MHz, DMSO) 3.2-3.4(m.2H); 3.7(s,3H); 4.4(t,1H); 8.6-9.2(m,6H)

MS ESP+ (mH)+ 119



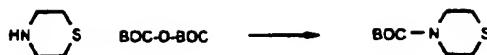
10 A solution of N-tert-butyloxycarbonyl thiomorpholine sulphone (14.805g, 63mmole) in trifluoroacetic acid (100ml) was stirred at room temperature for 45 minutes. Evaporation of the solvent in vacuo afforded a yellow oil, which was dissolved in ether (500ml). The required product separated as colourless crystals, which were filtered off, washed with ether (75ml) and dried in vacuo. The yield was 17.55g. 100%.

15 NMR (300MHz, CDCl₃) 3.4-3.5(m,4H); 3.5-3.6(m,4H)



20 A solution of metachlorobenzoic acid (55%. 21.7g) in chloroform (100ml) and dichloromethane (100ml) was added gradually over 40 minutes to a stirred solution of N-tert-butyloxycarbonyl thiomorpholine (6.4g, 31.5mmole) in chloroform (500ml) kept below 20°C. The cooling bath was removed and the mixture was stirred at room temperature for 1 hour. The mixture was washed with aqueous sodium hydroxide(2M. 2X300ml) and water (300ml). The organic solution was dried over magnesium sulphate and the solvent evaporated in vacuo to yield the required product as a colourless solid (7.50g, 100%).

25 NMR (300MHz, CDCl₃) 1.5(s,9H); 2.9-3.1(m,4H); 3.8-4.0(m,4H)



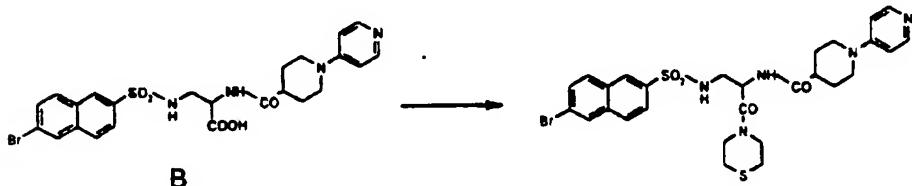
A solution of BOC-O-BOC (28.34g, 0.13Mole) in dichloromethane (100ml) was added over 15 minutes to a solution thiomorpholine (13.05ml, 0.13Mole) and triethylamine 5 (20.87ml, 0.15Mole) in dichloromethane (600ml). The mixture was stirred for 1 hour. Vigorous evolution of carbon dioxide occurred. Ether (600ml) was added and the organic solution was washed with citric acid (3X300ml, 1M), water (3X300ml), brine (300ml), dried over magnesium sulphate, and evaporated in vacuo to give N-tert-butyloxycarbonyl thiomorpholine as a colourless solid (26.5g, 100%).

10 NMR (300MHz,CDCl₃) 1.4(s,9H); 2.5-2.6(m,4H); 3.6-3.65(m,4H)

MS ESP+ (mH)+ 204

Example 2

1-(Thiomorpholino-4-carbonyl)-1-[1-(4-pyridyl)piperazin-4-ylcarbamoyl]-2-15 (bromonaphth-2-ylsulphonamido)ethane



To a stirred solution of B (2.5g, 3.652 mmole), thiomorpholine (0.442ml, 20 4.38mmole) and N-hydroxybenztriazole (0.7395g, 5.478mmole) in DMF (20ml) was added EDAC (0.840g, 4.38mmole). The solution was stirred overnight, and was then poured into water (300ml). This aqueous solution was adjusted to pH12 by the addition of aqueous sodium hydroxide, and extracted with ethyl acetate (3X200ml). The combined organic extracts were washed with water (300ml), brine (100ml), dried with magnesium 25 sulphate, and the solvent evaporated to yield the required product as a pale yellow solid (2.21g, 94%).

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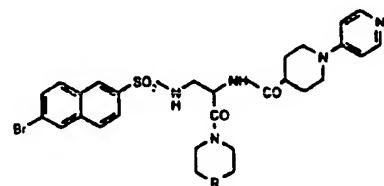
NMR (300MHz, DMSO) 1.4-1.5(m,2H); 1.6-1.7(m,2H); 2.3-2.5(m,2H); 2.7-2.9(m,3H);
 3.0-3.1(m,1H); 3.6-3.9(m,8H); 4.7-4.8(m,1H); 6.75(d,2H); 7.8(d,1H); 7.85(d,1H); 8.1-
 8.2(m,5H); 8.3(s,1H); 8.5(s,1H)

MS ESP+ (mH)+ 646

5

Example 3

Using similar procedures as described in Example 2 the following were prepared,
 but starting with piperidine and morpholine respectively in place of thiomorpholine.

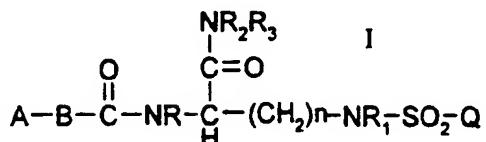


No	R	NMR(300MHz,DMSO)
1	CH ₂	1.3-1.7(m,10H); 2.3-2.45(m,1H); 2.7-2.95(m,3H); 3.0-3.1(m,1H); 3.2- 3.5(m,4H); 3.8-3.9(m,2H); 4.7-4.85(m,1H); 6.7-6.8(m,2H); 7.7-7.9(m,4H); 8.0-8.2(m,4H); 8.3(s,1H); 8.45(s,1H) MS ESP+ (mH)+ 628
2	O	1.4-1.5(m,2H); 1.6-1.7(m,2H); 2.3-2.4(m,1H); 2.5-3.0(m,4H); 3.0-3.1(m,1H); 3.2-3.6(m,7H); 3.8-3.9(m,2H); 4.7-4.8(m,1H); 6.7-6.8(m,2H); 7.7-7.9(m,3H); 8.0-8.2(m,5H); 8.3(s,1H); 8.5(s,1H) MS ESP+ (mH)+ 630

CLAIMS

1. A compound of formula I, or a pharmaceutically-acceptable salt thereof.

5



wherein:

10 A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur;

B is optionally substituted phenylene or a 6-membered heterocyclic ring containing 1, 2 or 3 nitrogen heteroatoms;

R and R₁ are independently selected from hydrogen and (1-4C)alkyl;

15 n is 1 or 2;

R₂ and R₃ are independently selected from hydrogen, (1-6C)alkyl, (4-7C)cycloalkyl, (2-6C)alkenyl on R₂ and R₃, may form along with the nitrogen to which they are attached a 5-, 6- or 7- membered heterocyclic ring which may contain in addition to the nitrogen atom present 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur, wherein

20 each R₂ or R₃ group or any heterocyclic ring formed from R₂ and R₃ may be optionally substituted by hydroxy, amino, carboxy, (1-4C)alkoxycarbonyl, oxo, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, or carbamoyl-(1-4C)alkyl;

Q is selected from phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl and a 5-, 6- or

25 7-membered heterocyclic ring containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur wherein Q may be optionally substituted by halo, halo(1-4C)alkyl, cyano, amino, hydroxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyoxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl,

30 N-(1-4C)alkylcarbonoyl, (2-6C)alkanoyl, (2-4C)alkanoylamino, hydroxy-(1-4C)alkyl,

(1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl wherein said phenyl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl or 5 benzoyl substituent bears 1, 2 or 3 substituents selected from halo, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-(1-4C)alkylcarbamoyl and (2-4C)alkenoylamino.

10 2. A compound of formula I as claimed in claim 1 wherein B is a 1,4-piperidinediyl or 1,4-piperazinediyl ring.

3. A compound of formula I as claimed in either claim 1 or 2 wherein Q is naphthyl.

15 4. A compound of formula I as claimed in claim 3 wherein Q is substituted by halo or (1-4C)alkyl.

5. A compound of formula I as claimed in any claim preceding claim wherein A is 4-pyrimidinyl or 4-pyridyl.

20

6. A compound of formula I as claimed in claim 5 wherein A is substituted by a substituent selected from halo, (1-4C)alkyl, amino and (1-4C)alkylamino.

7. A compound of formula I, as defined in any of the preceding claims, for use in 25 medical therapy.

8. A pharmaceutical composition comprising a compound of formula I, as defined in any claim from 1 to 6, and a pharmaceutically acceptable diluent or carrier thereto.

9. Use of a compound of formula I, as defined in any claim from 1 to 6, in the manufacture of a medicament for use in treating a Factor Xa mediated disease or medical condition.
10. A method of treating a FXa mediated disease or medical condition which comprises administering to a warm-blooded animal requiring such treatment an effective amount of a compound of formula as claimed in any claim from 1 to 6.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02290

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/14 A61K31/54 C07D491/04 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 20468 A (BOEHRINGER MANNHEIM GMBH) 15 September 1994 see claims 1,2,4-7,10,11 ---	1-9
Y	WO 96 10022 A (ZENECA LIMITED) 4 April 1996 see claims 1-7,9,10 ---	1-9
P,Y	WO 97 29104 A (ZENECA LIMITED) 14 August 1997 see claims 1-4,6,7 ---	1-9
P,Y	WO 98 21188 A (ZENECA LIMITED) 22 May 1998 see the whole document ---	1-9 -/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "D" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

23 October 1998

Date of mailing of the international search report

19.11.98

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Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02200

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ZAORAL M. & SORM F.: "Amino acids and peptides. LIX. Synthesis and some biological properties of L-DAB₂-vasopressin" COLLECT. CZECH. CHEM. COMMUN., vol. 31, 1966, pages 90-95, XP002081879 see compound II, page 95 -----</p>	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/02200

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 10 because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Appl. No.
PCT/GB 98/02200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9420468	A 15-09-1994	DE 4306873 A AU 6282494 A CA 2157215 A EP 0687254 A JP 8509472 T ZA 9401522 A	08-09-1994 26-09-1994 15-09-1994 28-12-1995 08-10-1996 04-09-1995
WO 9610022	A 04-04-1996	AT 168685 T AU 696491 B AU 3530795 A BR 9509045 A CA 2197471 A CZ 9700893 A DE 69503647 D EP 0783500 A ES 2119472 T HU 77769 A JP 10506122 T NO 971415 A PL 319430 A SK 38597 A ZA 9508085 A	15-08-1998 10-09-1998 19-04-1996 30-09-1997 04-04-1996 16-07-1997 27-08-1998 16-07-1997 01-10-1998 28-08-1998 16-06-1998 22-05-1997 04-08-1997 10-09-1997 24-04-1996
WO 9729104	A 14-08-1997	AU 1553497 A	28-08-1997
WO 9821188	A 22-05-1998	AU 4874897 A	03-06-1998

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0 printing error(s) detected.

36 patent page(s) printed on 36 page(s).